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Effects of Vasodilators and Peritoneal Dialysis Solution on the Microcirculation of the Rat Cecum (40606)[1]

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The addition of various vasodilators to peritoneal dialysis solutions has been shown to increase solute clearances during peritoneal dialysis (1–3). Presumably, one possible mechanism for this effect would be through vasodilation thus increasing solute delivery through an increase in tissue blood flow (4, 5). However, significant vasodilation in intestinal microcirculatory preparations has sometimes been difficult to demonstrate under resting conditions. Some investigators (6) have observed only minimal vasodilation of arterioles in the rat mesocecum preparation with PGE_1 that was not dose dependent and no dilation with PGA_1. Others (7, 8) have shown that isoproterenol and other vasodilators will produce dilation (usually 10–30%) at various levels of the microcirculation in the mesocecum but have also suggested that in general, vessels of this preparation are usually near maximally dilated by circulating epinephrine (7). In intestinal wall preparations, dilation has been demonstrated in vessels preconstricted with norepinephrine (9) and has been reported not to be a significant microvascular factor with 10^{-8} g/ml isoproterenol (10).

The present study was designed to determine if concentration dependent vasodilatory responses could be elicited in the vasculature of another microcirculatory preparation located in the peritoneum. Thus, we determined the responses to three different vasodilators (sodium nitroprusside, papaverine, and isoproterenol) on small arteries and veins on the mesothelial surface of the rat cecum. These responses were compared to those obtained with a commercial dialysis solution with and without nitroprusside.

Methods. Sprague–Dawley rats (134–158 g) were anesthetized with an intraperitoneal injection of a combination of α-choralose (60 mg/kg) and urethane (800 mg/kg). A small midline incision was made in the abdominal cavity and the cecum was exteriorized with intact blood and nerve supply. It was split along its midline and spread over an optical port in a 60-ml Plexiglas tissue bath. The bath was filled with a modified Krebs solution containing NaCl (118.5 m*M*), $NaHCO_3$ (19.9 m*M*), dextrose (11.6 m*M*), KCl (4.7 m*M*), $CaCl_2 \cdot 2H_2O$ (2.5 m*M*), KH_2PO_4 (1.2 m*M*), and $MgSO_4 \cdot 7H_2O$ (1.2 m*M*). Bath temperature was controlled at 37°C by means of an immersed insulated heating coil. The pH of the bath was maintained at 7.4, by bubbling carbon dioxide into the Krebs solution. The rat and tissue bath were positioned on a microscope stage so that light passed through the optical port and cecum into the microscope objective. Closed-circuit television microscopy was used and the diameters of a small artery (~70 μm) and small vein (~140 μm) on the mesothelial surface of the cecum were measured simultaneously by an automated device previously developed in our laboratory (11).

The left femoral artery was cannulated for measurement of mean arterial pressure and small subcutaneous needle electrodes were used to obtain an electrocardiogram for heart rate calculations. Blood pressure and heart rate were recorded every minute. Rectal temperature was maintained by a small heating pad placed under the animal.

One group of animals was used to determine the vascular responses to a commercially available dialysis solution (McGaw). After a 10-min control period in Krebs solu-

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tion, the bath was drained and dialysis solution (pH adjusted to 7.4 with sodium hydroxide) with or without nitroprusside was added and the effects were observed for 45 min. In another group of rats, concentration–response curves to isoproterenol HCl, sodium nitroprusside, and papaverine HCl were determined. In these experiments there was a 10-min control period in just Krebs solution and a 5-min experimental period with each concentration of each drug in Krebs solution. Every 5 min the drug concentration was increased to obtain the concentration–response curve. The order of these curves was varied among experiments and there was at least a 20-min wash period in Krebs solution in between concentration–response curves to allow the vessels to return to near control diameters.

Results. The mean diameters during each control period of the small artery and paired vein are shown in Table I. Within each group, there were no significant differences between small artery control diameters and between small vein control diameters.

The effect of McGaw dialysis solution without and with nitroprusside (1×10^{-5} *M*) on small arteries on the mesothelial surface of the rat cecum are shown in Figure 1. Dialysis solution alone produced dilation which was approximately 35% above the control diameters. The same level of dilation was present for the duration of the experimental period. The combination of dialysis solution and nitroprusside produced essentially the same response as dialysis solution alone with no differences in the maximal increase in the diameter of the arteries. On the small vein (Fig. 2) dialysis solution produced a 45% dilation above control diameters. However, the addition of nitroprusside produced a dramatic increase in the maximal dilation. There was over a 100% increase from control diameters.

TABLE I. SMALL VESSEL CONTROL DIAMETERS

	Artery ($\bar{x}$ ± SEM μM)	Vein ($\bar{x}$ ± SEM μM)
Group I		
McGaw (n = 8)	75 ± 2.6	144 ± 6.1
McGaw plus nitroprusside (n = 8)	78 ± 2.0	132 ± 8.5
Group II		
Isoproterenol (n = 7)	67 ± 3.3	141 ± 11.5
Nitroprusside (n = 11)	64 ± 2.6	135 ± 10.7
Papaverine (n = 7)	68 ± 5.9	141 ± 12.7

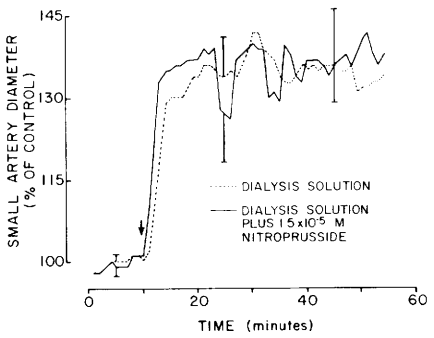

FIG. 1. These curves represent the small artery response ($\bar{x}$ ± SEM) to McGaw dialysis solution with and without nitroprusside in eight experiments. After a 10-min control period in Krebs solution, the bath is drained (at the arrow) and the cecum is exposed to dialysis solution for 45 min.

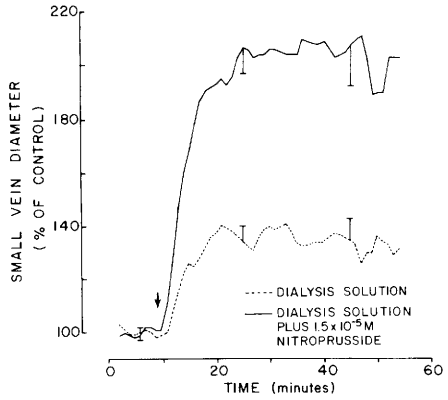

FIG. 2. These curves represent the small vein response ($\bar{x}$ ± SEM) to McGaw dialysis solution with and without nitroprusside in eight experiments. After a 10-min control period in Krebs solution, the bath is drained (at the arrow) and the cecum is exposed to dialysis solution for 45 min.

In the second group of rats the concentration–response relationship to three vasodilators, isoproterenol, nitroprusside, and papaverine were determined in the small arteries and veins of the cecum (Fig. 3). Complete concentration–response curves were obtained with isoproterenol and nitroprusside, however, because of solubility problems at concentrations of papaverine greater than 10^{-3} *M*, concentration–response curves could not be completed with this drug. Group data are given in Table II. With all three drugs at the maximally effective concentration (maximum

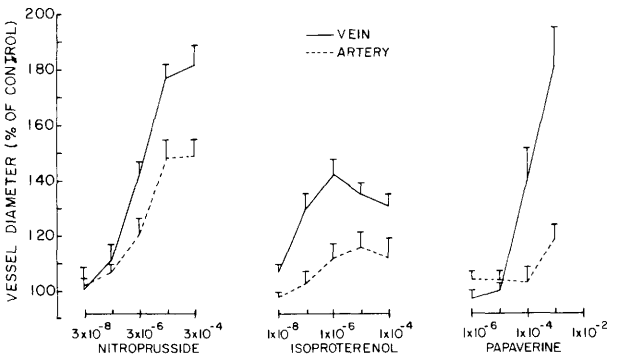

FIG. 3. Concentration–response curves were determined for three vasodilators on small arteries and veins in the rat cecum. Group data ($\bar{x} \pm$ SEM) is plotted as a percentage of the mean diameter during the control period preceding each curve.

TABLE II. SMALL VESSEL DILATION

	Maximum dilation (%)			pD_2		
	Artery		Vein	Artery		Vein
Isoproterenol (7)	21 ± 6.3 *	*	48 ± 2.7 *	6.3 ± 0.28 *	*	7.1 ± 0.17 *
Nitroprusside (11)	52 ± 6.4 *	*	84 ± 6.9 NS	5.6 ± 0.27 *	NS	5.6 ± 0.16 *
Papaverine (7)	20 ± 4.6	*	81 ± 14.1	3.9 ± 0.31	NS	3.9 ± 0.11

* $P < 0.05$ analysis of variance with Duncan's multiple range test for unequal N size.

dilation (%)), small vein dilation was significantly greater than small artery dilation. In addition, maximum dilation produced by nitroprusside in the vein was significantly greater than that produced by isoproterenol (84 vs 48%). Dilation produced by nitroprusside in the artery was significantly greater than that produced by isoproterenol and papaverine (52 vs 21 and 20%). In this table, sensitivity is expressed as a pD_2 value ($pD_2 = -\log ED_{50}$). Thus the higher the pD_2 the more sensitive is the vessel to the vasodilator. These three drugs appeared to have the same potency order for both the artery and the vein (isoproterenol > nitroprusside > papaverine). The values for papaverine were calculated by considering the response at 10^{-3} M to be maximal. A higher maximum would have further decreased the pD_2 value but kept the potency order the same. For the comparison of arteries and veins a difference in sensitivity was only seen for isoproterenol. The small vein ($pD_2 = 7.1 \pm 0.17$) was more sensitive to isoproterenol than the small artery ($pD_2 = 6.3 \pm 0.28$).

Discussions. Our *in vivo* data demonstrates that the small veins and arteries on the mesothelial surface of the rat cecum have a significant basal level of tone. The small veins may dilate as much as 100% and the small arteries 45% (Figs. 1 and 2) in response the peritoneal dialysis solution with nitroprusside. This contrasts with some *in vitro* preparations of larger vessels which have no basal tone and which must be preconstricted by a vasoconstrictor agent before the effects of a vasodilator can be demonstrated (12). It also contrasts with *in vivo* mesocecum preparations where vasodilation was minimal as assessed by the application of prostaglandin on ~20-μm arterioles (6) or in larger vessels (~40-μm arterioles and ~45-μm venules) in response to four different vasodilators (7) including isoproterenol. Thus, these mesocecum mesenteric vessels may serve solely as conduits and may not be responsive to vasodilatory inputs during peritoneal dialysis whereas the vessels on the intestinal wall, as we have shown, may dilate in response to peritoneal dialysis solutions. Alternatively, tone in these representatives of visceral peritoneum (the mesentery of the mesocecum or the mesothelial surface of the intestinal wall) may be present only in larger vessels such as

we have examined in this study.

The predominant effects of peritoneal dialysis solution in our model of visceral peritoneum (the mesothelial wall of the cecum) is vasodilation of both the small artery and small vein. This effect is similar to that previously shown for arterioles in the cremaster muscle (4). This muscle is derived from abdominal wall skeletal muscle and may represent the behavior of arterioles in parietal peritoneal vasculature. In our current experiments, the addition of nitroprusside to dialysis solution produced no additional dilation of the small artery but increased dilation in the small veins from 40 to 100% (Figs. 1 and 2). Thus, dialysis solution appears to produce maximal dilation of the small artery but less than half maximal dilation of the small vein.

The *in vivo* concentration response curves demonstrated that there is a significantly greater maximal dilation in the vein than in the artery with all three vasodilators and that there are large differences in potency (pD_2 values) among the three vasodilators with isoproterenol > nitroprusside > papaverine (Table II). These data also show that nitroprusside and papaverine were equally efficacious for dilation of the vein. Both drugs produced about a 80% dilation of this vessel. This suggests that nitroprusside does not have a unique effect on the vein. Both these nonspecific vasodilators produced significantly greater maximal dilation on the vein than isoproterenol. Thus, maximal β-adrenergic receptor activation by the use of isoproterenol does not produce maximal vein dilation.

At comparable states of vein dilation, nitroprusside produces significantly greater small artery dilation than the other two vasodilators. Thus the combination of venous and arterial dilation for nitroprusside may be uniquely greater than for other vasodilators and may also be involved in the mechanism(s) of greater increases in solute clearances during peritoneal dialysis observed with nitroprusside in comparison to other vasodilators (1).

Summary. Peritoneal dialysis solutions produce vasodilation of small arteries and veins on the mesothelial surface of the rat cecum. Dilation in the artery is not altered by the addition of nitroprusside to the dialysis solution. However, there is a dramatic increase in dilation of the small vein upon addition of nitroprusside. This small vein phenomena is not unique to nitroprusside since papaverine can produce dilation of equal magnitude. However, of the three vasodilators tested (nitroprusside, papaverine, and isoproterenol), at comparable vein dilation, nitroprusside produced the greatest small artery dilation. Thus, a unique combination of small vein and small artery mechanisms may in part explain the increases in clinical clearances observed with the addition of nitroprusside to dialysis solution.

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